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09/990,586	11/21/2001	Hing C. Wong	71758/46943-CIP2	2050

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,586	WONG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *59-61 and 63-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-58 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-72 are pending.

2. Applicant's election with traverse of Group I, claims 1-58 and 62 drawn to a humanized antibody that binds specifically to human tissue factor (TF), comprises HC-FR1-4, HC-CDR1-3, LC-FR1-4, LC-CDR1-3, HC constant sequence, LC constant region, fragments thereof and a composition thereof and LC constant region of SEQ ID NO: 97, HC constant region of SEQ ID NO: 98, hOAT isotype, HC CDR2 of SEQ ID NO: 101, HC FR1, FR2, FR3 and FR4 of SEQ ID NO: 91, LC FR1, FR2, FR3 and FR4 of SEQ ID NO: 79 as the species of specific antibody filed on 12/08/03, is acknowledged.

Applicant's traversal is on the grounds that searching Group II along with Group I will not pose an undue burden on the Office as a search of the art is expected to be overlapping for both groups. Further Applicant argues that recent advances in computer searching technology will assist the Office in its search of the art. This is not found persuasive because nucleic acids of Group II and antibodies of Group I differ with respect to their structures and physicochemical properties which are recognized divergent subject matter. Therefore the an isolated nucleic acid encoding at least one of the heavy or light chain of humanized antibody that binds specifically to human tissue factor of Group II and the humanized antibody that binds specifically to human tissue factor (TF) of Group I are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 59-61 and 63-72 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-58 and 62 are under examination as they read on a humanized antibody that binds specifically to human tissue factor (TF).

5. The specification on page 1 should be amended to recite the U.S. Provisional Application USSN 60/343,306 and to reflect the status of 09/293,854 and the relationship between 09/293,854 and the instant application.

6. The oath is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath submitted on 11/13/02 is defective because: Residence of inventor Esperanza Liliana Nieves has been altered without being initialed and dated.

7. Claim 7 is objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim (i.e. claim 7) cannot depend from any other multiple dependent claim (i.e., claims 3-6).

8. Claims 10-13 are objected to under 37 CRD 1.821(d) because it lacks an amino acid sequence identifier.

9. Claim 19 is objected to for the following informalities: Claim 19 recites "as least one", the word "as" should be "at". Correction is required.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 19-20, 27-42, 46-48 and 51-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 19 is indefinite in the recitation "further comprises at least one human framework (FR) region". Since the humanized antibody is whole antibody containing the FR then it is unclear how a humanized antibody would "further comprises" at least one human FR region. It is unclear how a humanized antibody would "further comprises" at least one human framework (FR) region.

B. Claims 46-48 and 51-52 are indefinite in the recitation "further comprises/comprising". Since the humanized antibody is whole antibody containing the light chain and the heavy chain then it is unclear how a humanized antibody would "further comprises" on the light/heavy chain. It is suggested that Applicant uses "wherein" for example in claim 47, "The antibody of claim 45, wherein the light chain constant sequence comprises SEQ ID NO 97 or SEQ ID NO: 99".

C. Claim 46 is indefinite because Claim 46((j) recites CDR3 amino acid sequence shown in Figure 12(C) (SEQ ID NO:6), however, Figure 12(C) represents CDR2. It appears that the claim should recite Figure 12(D) (SEQ ID NO:7).

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Applicant's statement, filed 10/21/02 (Paper No. 22), in parent Application No. 09/293,854, satisfies the requirement for the deposit of the biological material H36.D2.B7 (ATCC HB-12255) recited in claims 4 and 5 under 35 USC § 112, first paragraph.

14. Claims 1-50, 55-58 and 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody that binds specifically to TF, wherein said antibody comprising the LC constant region is SEQ ID NO: 97 or 99, HC constant region is SEQ ID NO: 98 or 100, the antibody has an IgG1 (hOAT) or IgG4 (hFAT) isotype, HC CDR2 is SEQ ID NO: 90 or 101 or a specific change such as in claims 28, 30, 32 or 34, HC FR1, FR2, FR3 and FR4 of SEQ ID NO: 91, LC FR1, FR2, FR3 and FR4 of SEQ ID NO: 79 or a specific change such as in claims 36, 38, 40 or 42 (such as the antibody recited in claims 51-54) for inhibiting TF-initiated coagulation, does not reasonably provide enablement for any humanized antibody that binds specifically to human tissue factor (TF) to form a complex, wherein factor X or factor IC binding to the complex and the FX or FIC activation by TF:VIIa are inhibited in claim 1, wherein the antibody has a binding specificity for the TF about equal (to) or greater than the antibody obtained from cell line H36.D2.B7 deposited under ATCC Accession No. HB-12255 in claims 4-5, wherein the antibody comprises at least one fully murine complimentarily determining region (CDR), wherein the antibody has at least about 90% amino acid sequence identity to a human antibody in claim 8, wherein the variable region of the humanized antibody has at least about 70% aminop acid sequence identity to a human antibody variable region in claim 9; a humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FvIIa thereto is inhibited in claim 17, wherein all the CDR are murine in claim 18, wherein the antibody further comprises at least one human framework (FR) region 19, wherein the first CDR (CDR1), second CDR (CDR2) or third CDR (CDR3) of the heavy chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ I DNO:8, 9/101 or 10, respectively, in claims 21-23, wherein the first CDR (CDR1, second CDR (CDR2), or the third CDR (CDR3) of the light chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ ID NO:2, 6, 7, respectively, in claims 24-26, A fragment of the humanized antibody of claim 17, in claim 43, A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor C or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody comprising on the heavy chain: a) a first CDR (CDR1) which is "at least 95% identical to CDR1" amino acid sequence shown in Figure 13B(SEQ ID NO:8), (b0 a second CDR (CDR2) which is "at least 95% identical to CDR2" amino acid sequence shown in Figure 13C (SEQ ID NO: 9 or 101), c) a third CDR (CDR3) which is "at least 95% identical" to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO: 10) in claim 45, the antibody further comprising on the light chain h) a first CDR (CDR1) which "at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO:2), I) a second CDR(CDR2) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12C (SEQ ID NO: 6), J) a third CDR(CDR3) which is "at least 95% identical to the CDR3" amino acid sequence shown in Figure 12(C) (SEQ ID NO:6), in claim 46.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make and use humanized antibodies. Claim, 6 recites "at least one full murine CDR", claim 17 recites " at least one CDR", claim 8 recites "at least about 90% amino acid sequence identity to a human antibody", claim 9 recites "the variable region of the humanized antibody has at least 70% amino acid sequence identity to a human antibody variable region" claims 21-26, 45 and 46 recite "at least 95% identical to" CDRs. However, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (i.e., H36.D2.B7). It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that humanized antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of a tissue factor (TF) antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce humanized antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanize antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (US Patent 6,632,927) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (col.2 lines 58-61). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

Claims 4-5, recite a binding specificity for the TF about equal (to) or greater than the antibody obtained from the cell line H36.D2.B7, however the specification does not defined the term "binding specificity" nor does the specification provides guidance on how to obtain humanized antibodies that has a binding specificity for the TF.

Claims 1-9, 17 recite that the "humanize" antibodies involved grafting a murine CDR onto the framework and constant domain of a human antibody. However, such grafting are often

unsuccessful because the human framework distorted the shape of the CDRs, resulting in loss of binding specificity.

Claims 10, 12, 27, 29, 31, 33, 35, 37, 39, 41, 45 and 46 recite at least 95% amino acid sequence identity to the FR sequences. However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. The specification does not enable one skill in the art at the time the invention was made to predict the structure of a specific antibody and identify the few key amino acids in the framework necessary to retain the shape, and thus the binding specificity, of the CDRs. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

15. Claims 1-50, 55-58 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a humanized antibody that binds specifically to TF, wherein said antibody comprising the LC constant region is SEQ ID NO: 97 or 99, HC constant region is SEQ ID NO: 98 or 100, the antibody has an IgG1 (hOAT) or IgG4 (hFAT) isotype, HC CDR2 is SEQ ID NO: 90 or 101 or a specific change such as in claims 28, 30, 32 or 34, HC FR1, FR2, FR3 and FR4 of SEQ ID NO: 91, LC FR1, FR2, FR3 and FR4 of SEQ ID NO: 79 or a specific change such as in claims 36, 38, 40 or 42 (such as the antibody recited in claims 51-54) for inhibiting TF-initiated coagulation

Applicant is not in possession of any humanized antibody that binds specifically to human tissue factor (TF) to form a complex, wherein factor X or factor IC binding to the complex and the FX or FIC activation by TF:VIIa are inhibited in claim 1, wherein the antibody has a binding specificity for the TF about equal (to) or greater than the antibody obtained from cell line H36.D2.B7 deposited under ATCC Accession No. HB-12255 in claims 4-5, wherein the antibody comprises at least one fully murine complimentarily determining region (CDR), wherein the antibody has at least about 90% amino acid sequence identity to a human antibody in claim 8, wherein the variable region of the humanized antibody has at least about 70% aminop acid sequence identity to a human antibody variable region in claim 9; a humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor X or factor IX binding to TF or TF:FVIIa and activation by TF:FvIIa thereto is inhibited in

claim 17, wherein all the CDR are murine in claim 18, wherein the antibody further comprises at least one human framework (FR) region 19, wherein the first CDR (CDR1), second CDR (CDR2) or third CDR (CDR3) of the heavy chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ I DNO:8, 9/101 or 10, respectively, in claims 21-23, wherein the first CDR (CDR1, second CDR (CDR2), or the third CDR (CDR3) of the light chain hypervariable region is at least 95% identical to the CDR1, CDR2 or CDR3 amino acid sequence of SEQ ID NO:2, 6, 7, respectively, in claims 24-26, A fragment of the humanized antibody of claim 17, in claim 43, A humanized antibody comprising at least one murine complementarity determining region (CDR), wherein the antibody binds specifically to human tissue factor (TF) to form a complex, and further wherein factor C or factor IX binding to TF or TF:FVIIa and activation by TF:FVIIa thereto is inhibited, the antibody comprising on the heavy chain: a) a first CDR (CDR1) which is "at least 95% identical to CDR1" amino acid sequence shown in Figure 13B(SEQ ID NO:8), (b0 a second CDR (CDR2) which is "at least 95% identical to CDR2" amino acid sequence shown in Figure 13C (SEQ ID NO: 9 or 101), c) a third CDR (CDR3) which is "at least 95% identical" to the CDR3 amino acid sequence shown in Figure 13D (SEQ ID NO: 10) in claim 45, the antibody further comprising on the light chain h) a first CDR (CDR1) which "at least 95% identical to CDR1 amino acid sequence shown in Figure 12B (SEQ ID NO:2), I) a second CDR(CDR2) which is at least 95% identical to CDR1 amino acid sequence shown in Figure 12C (SEQ ID NO: 6), J) a third CDR(CDR3) which is "at least 95% identical to the CDR3" amino acid sequence shown in Figure 12(C) (SEQ ID NO:6), in claim 46.

Applicant has disclosed only humanized anti-TF of H36.D2.B7 deposited under ATCC Accession No. HB12255; therefore, the skilled artisan cannot envision all the contemplated humanized antibodies against TF sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath

at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

17. Claim 1-9, 14-20, 43-44, 55-57 and 62 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 96/40921 (IDS Ref. No. BB).

The `921 publication teaches a humanized antibody that binds specifically to human tissue factor (TF) and the ability of the CDR-grafted antibody to inhibit factor X activation, provides a measure of the ability of the CDR-grafted antibody to inhibit the activity of human tissue factor (see page 19, lines 1-6 in particular). The `921 publication teaches that the CDR-grafted antibodies are capable of inhibiting human tissue factor wherein the CDRs are derived from a non-human monoclonal antibody against tissue factor and the FR and C regions are derived from one or more human antibodies (see page 8, line 29 through page 9, line 4 in particular). In addition, the `921 publication teaches that FR region can retain the human FR residue at residues 6, 17, 68, 73 and 78 of the heavy chain and residues 39, 41, 116 and 105 of the light chain. The `921 publication further teaches that the heavy chain constant region and the light chain constant region is the human IgG4 constant region and the human IgG4 Kappa constant region, respectively (see page 16, lines 10-14 in particular). Further, the `921 publication teaches active fragments of the CDR-grafted antibodies, and in particular Fab fragments and F(ab')2 fragments (see page 16, lines 14-25 and published claim 18, page 92 in particular). The `921 publication teaches that the CDR-grafted antibody wherein the antibody is a murine antibody (monoclonal) (see published claim 2, page 90). Finally, the `921 publication teaches a pharmaceutical compositon comprising at least one CDR-grafted antibody capable of inhibiting human tissue factor and a pharmaceutically acceptable carrier (see published claim 36 in particular).

While the prior art teachings may be silent as to the "wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of <15 nM" in claim 3 per se; the antibodies in the reference is the same as the claimed antibodies. Therefore these limitations are considered inherent properties. Specially, because FX binds to a catalitically active complex that includes tissue factor.

Since the office does not have a laboratory to test the reference humanized antibodies, it is applicant's burden to show that the reference antibody does not bind to the TF about equal to or greater than the antibody obtained from cell line H36.D2.B7 recited in the claim. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-6, 8-9, 55-58 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Application No, 5,223,427 A (IDS Ref. No. AA) in view of Owens *et al* (1994).

The `427 patent teaches monoclonal antibodies TF9-1B8, TF9-5B7, TF8-5C4, TF8-11D12 and TF8-21F2 that immunoreact with human Tissue factor (col, 32-35, examples 5-7, and col. 41, Example 14 in particular). The `427 patent further teaches a composition comprising the antibody that can be formulated into the therapeutic compostion as neutralized pharmaceutically acceptable salt forms or in association with the required diluent; i.e, carrier or vehicle (see col., 23 lines 42-65 in particular).

The claimed invention differs from the reference teaching only by the recitation of a humanized antibody ,a Fab fragment, a $F(ab')_2$ fragment or in claims 1-6, 8-9 and 55-58.

Owens *et al* teach the modification of murine antibodies such as a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody using monoclonal antibody technology. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement –dependent cytotoxcity (see the entire document).

While the prior art teachings may be silent as to the "wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of <15 nM" in claim 3 per se; the antibodies in the reference is the same as the claimed antibodies. Therefore ""wherein factor X or IX binding to the complex and the FX or FIX activation by TF:VIIa are inhibited" in claim 1, " the antibody has a dissociation constant (Kd) for the TF of less than about 0.5 nM" in claim 2, " the antibody is further characterized by increasing blood clotting time by at least about 5 seconds as determined by a standard prothrombin (PT) clotting assay at an antibody concentration of <15 nM" in claim 3 are considered inherent properties. Specially because FX binds to a catalitically active complex that includes tissue factor.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by the `427 patent as humanized antibody, Fab and $F(ab')_2$ fragments of the humanized antibody as taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and because the antibody fragments are the reagents of choice for some clinical applications as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-9, 15-18, 21-23, 25-26, 43-44, 55-58 and 62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-39 of U.S. Patent No. 6,555,319. Although the conflicting claims are not identical, they are not patentably distinct from each other because both the `319 patent and the instant application are claiming the same humanized antibody, even though the `319 patent claims a humanized chimeric antibody that binds native human tissue factor to form a complex. Specially because the instant application claims are silent with regard to the FRs, while the `319 patent claims "humanized chimeric antibody". Chimeric antibodies are obtained by joining the antigen-binding variable domains of a mouse monoclonal antibody (mAb) to human constant domains: mouse V_L to human C_L and mouse V_H to human C_H1-C_H2-C_H3 for light and heavy chain, respectively. Humanized antibodies are generated by grafting the antigen-binding loops, CDRs, from a mouse mAb into a human IgG. Further, the first humanized antibodies were chimeric antibodies. Therefore, the instant claims read on a "humanized chimeric antibody".

22. No claim is allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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March 5, 2004

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